UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/288,719	04/09/99	KONTERMANN R	26083/201

HM12/0119

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EXAMINER	
BECKERLEG, A	
ART UNIT	**PAPER NUMBER**
1632	16

DATE MAILED: 01/19/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/288,719	KONTERMANN ET AL.	
	Examiner	Art Unit	
	Anne M Beckerleg	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-82* is/are pending in the application.

4a) Of the above claim(s) *5,19-22,24,30-52,54-71,73-77,79-82* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-18, 23, 25-29, 53, 72, and 78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892) ✓

16)☒ Notice of Draftsperson's Patent Drawing Review (PTO-948) ✓

17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,8,9,10* . ✓

18)☐ Interview Summary (PTO-413) Paper No(s). _____ .

19)☐ Notice of Informal Patent Application (PTO-152)

20)☐ Other:

DETAILED ACTION

Applicant's response received on 11/3/00 to the restriction requirement mailed on 10/4/00 has been entered. Applicant has elected with traverse invention I, claims 1-55, 72, and 76-78. The applicant argues that inventions I and II should be recombined as it would not be an undue burden on the examiner to search both invention. The restriction requirement mailed on 10/4/00, paper no. 13, provided a detailed explanation of why the groups should be restricted based on the properties of single chain binding molecules versus vectors encoding single chain binding molecules and on the significant differences involved in methods of using single chain binding proteins versus vectors encoding single chain binding proteins. The applicant has not provided any specific arguments concerning these issues. As such, the restriction requirement is made **final**.

In addition to the restriction requirement between inventions I and II, the applicant was required to elect a single species from each of groups 1) - 4). The applicant elected the following: for group 1) the cell membrane of a target cell; for group 2) a vector; for group 3) a prodrug activating enzyme; and for group 4) prophylaxis or treatment of cancer. In view of applicant's elected species, claims 5, 19-22, 24, 30-52, 54-55, and 76-77 are directed to non-elected species of the invention. Therefore, claims 5, 19-22, 24, 30-52, 54-71, and 73-77, and 79-82 of the instant application are withdrawn from prosecution as being drawn to an invention and/or species nonelected with traverse in Paper No.15 . A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP

§ 821.01. Claims 1-4, 6-18, 23, 25-29, 53, 72, and 78 are active in the instant application. An action on the merits follows.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-18, 23, 25-29, 53, 72, and 78 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification discloses the construction of single chain binding molecules comprising a variable domain of a heavy chain of an immunoglobulin (VH) with a first specificity (A), a variable domain of a light chain of an immunoglobulin (VL) with a first specificity (A),a variable domain of a heavy chain of an immunoglobulin (VH) with a first specificity (B), a variable domain of a light chain of an immunoglobulin (VL) with a first specificity (B), wherein the VH and VL domains are connected in the form of a VH-VL construct or VL-VH construct, and wherein the two VH-VL constructs are connected via a peptide (P).

The specification further discloses that the first specificity (A) can be towards the cell surface of a target cell, such as a cancer cell, and the second specificity (B) can be towards a vector. In addition, the specification discloses that the single chain binding molecule can further comprise an effector (E) linked to said molecule by a connector (B) such that the connector comprises a protease cleavage site and the effector is a prodrug activating enzyme. The specification provides several uses for the instant single chain molecules ranging from their use in the diagnosis of disease to the treatment or prophylaxis of cancer. In a preferred embodiment of the invention, the specification states that single chain binding molecules with dual specificity for a target cell and a vector can be used as ligand for target cell-specific binding and internalization of the vector.

The specification does not provide an enabling disclosure for making a single chain binding molecule with dual specificity for the cell membrane of a target cell and a vector. The specification does not provide any description, methods for identifying, or methods of making any naturally occurring antibody wherein the VH and VL domains recognize a component of any vector, whether plasmid or viral based. Further, the specification does not provide guidance for synthesizing or engineering VH and VL domains to recognize a component of a vector. It is also noted that the specification does not attempt to incorporate by reference any publication which lists such antibodies or Fv fragments or provide citations for any such references. The specification's disclosure is limited to the statement that it is advantageous for the second specificity (B) to be against a vector, particularly a viral vector derived from adenovirus, adeno-associated virus, vaccinia virus, RSV, HSV, Influenza virus, or lentivirus (specification, page 10,

lines 1-8). As for the working examples provided by the specification, the sole disclosed example of a single chain binding molecule binds to the carcinoembryonic antigen CEA and E. coli β-galactosidase. The applicant is reminded that the Federal Circuit has stated:

> a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art**. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

Further, based on the disclosed intended use of single chain binding molecules which bind to both the cell surface of a target cell and a vector to function as ligands for targeted vector delivery, the specification does not provide sufficient guidance as to the affinity and avidity of the vector binding VH and VL domains of the ligand to a vector and the affinity and avidity of the target cell binding VH and VL domains of the ligand that correlates with the targeting and binding of free vector to specific cells under *in vitro* or *in vivo* conditions. Also, the specification provides no guidance as to the physical or biological constraints affecting the uptake of ligated vector by the target cell. The majority of cells are limited to pinocytosis or receptor mediated endocytosis of extracellular material. Only macrophages and certain dendritic cells are capable of phagocytosis of large particles. The specification provides no guidance as to the identity or physical characteristics

of cells which are capable of taking up large molecular complexes or identify cellular receptors which can mediate the uptake of a vector ligated to a single chain antibody complex according to the instant invention. While it is noted that the specification mentions that a "fusogenic" peptide can be included in the composition to facilitate vector uptake at the target cell, the specification does not identify or describe any "fusogenic" peptide for use in the instant invention or demonstrate that the inclusion of any "fusogenic" peptide in the any single chain binding molecule/vector complex can be taken up by any bound target cell. In the applicant's *in vitro* working example, the single chain binding molecule which binds CEA and β-galactosidase does not appear to be taken up by the CEA expressing cells but rather remains on the cell surface of the target cells which express CEA. Thus, based on the lack of guidance provided by the specification as to the identity or characteristics of VH and VL domains which recognize a vector or component of a vector and which can be used to successfully bind free vector *in vitro* or *in vivo*, the lack of guidance as to the identity of cells capable of taking up single chain binding molecule /vector complexes, the identity of cell surface receptors capable of mediating endocytosis of said binding molecule/ vector complexes, or the identity of fusogenic peptides which are necessary to facilitate or mediate uptake of the vector complexes, the lack of working examples, and the breadth of the claims, it would have required undue experimentation to make and use any and all single chain binding molecules with a first specificity for the cell surface of a target cell and second specificity for a vector.

The specification does not provide an enabling disclosure for the treatment or prophylaxis of any disease including cancer by administering any and all single chain binding molecules with a first specificity for the cell surface of a target cell, such as a tumor cell, and second specificity for a vector by any route of administration. It is noted that the claims do not recite the administration of a vector. It is unclear in the absence of vector administration what possible therapeutic effect the single chain binding molecule itself could have on the target tumor cell. As discussed in detail above, the specification fails to provide an adequate description for making single chain binding molecules which bind to both a cell surface target molecule and a vector. The specification further fails to provide any guidance as to routes and methods of administration of vector and single chain binding molecule such that a therapeutic effect on a target cell is observed. The specification does not disclose whether the vector and single chain binding molecule are prebound *in vitro* prior to administration to the host or whether the single chain binding molecule is expected to encounter and bind both vector present at any location in the host and a target cell which may be present at a site distal from that of the vector. Further, the therapeutic potential of any compound *in vivo* is significantly affected by the physiological conditions at the site of administration, i.e. oral versus subcutaneous, the rate of clearance of the compound, i.e. subcutaneous versus intravenous, and the half-life and stability of the compound under physiological conditions. The specification does not provide any guidance as to any of these aspects of therapeutic gene or protein delivery. Finally, the specification provides no guidance as to the nature of the gene(s) encoded by the targeted vector which are to have a therapeutic effect or teach the level of target cell transfection

and expression of the encoded gene that would have any effect on tumor formation or tumor growth.

At the time of filing , the skilled artisan did not consider the targeting of vectors to specific cell types *in vivo* to be predictable . Deonarain, in a review entitled, " Ligand-targeted receptor-mediated vectors for gene delivery", teaches that one of the main obstacles to successful gene therapy is, " ... the ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time", and states that, " .. even after almost 30 years of relentless pursuit, nothing has yet delivered such a promise in terms of clinical results" (Deonarain et al. (1998) Exp. Opin. Ther. Patents, Vol. 8 (1), page 53, lines 1-4, and page 54, lines 12-15). Miller et al. concurs, teaching that the development of surface targeting has been problematic and that the biggest challenge in targeted vector design is to combine targeting with efficiency of gene expression, since , " attainment of one usually compromises the other" (Miller et al. (1995) FASEB, Vol. 9, page 198, paragraph 2). The specification does not provide guidance in the form of detailed teachings or specific working examples for methods to target any vector to any particular cell type or to tumors or cells expressing tumor antigens in particular. Therefore, in view of the art recognized unpredictability in achieving targeted gene delivery *in vivo* using vectors currently available at the time of filing, the absence of guidance provided by the specification for any of the conditions and parameters under which a therapeutic effect on cancer could be achieved *in vivo* using the disclosed single chain binding molecules with dual specificity for a vector and a target cell, and the breadth of the claims, it would have required

undue experimentation for the skilled artisan to prevent or treat cancer according to the instant invention.

The claims are free of the prior art of record as the prior art of record does not specifically teach a single chain binding molecule wherein a binding specificity recognizes the cell surface of a target molecule and a second binding specificity recognizes a vector. The closest prior art of record is represented by Gruber et al. (1994) J. Immunol., Vol. 152 (11), 5368-5374. Gruber et al. teaches the construction of scFv(2) wherein the Fv heavy and light chain domains of a first antibody with specificity for the T cell receptor on T cells is joined by a 25 amino acid residue linker to the Fv heavy and light chain domains of a second antibody with specificity for fluorescein. However, Gruber provides no motivation for generating an scFV(2) wherein one of the specificities is for a vector component. Further, the prior art of record teaches that at the time of filing, the methods for targeting vectors to specific cells were focusing on the engineering of the vector itself to express a monoclonal antibody which recognized a cell surface molecule on a target cell.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be

reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Karen Hauda, can be reached at (703) 305-6608. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The official fax number is (703) 308-4242.

Dr. A.M.S. Beckerleg